

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

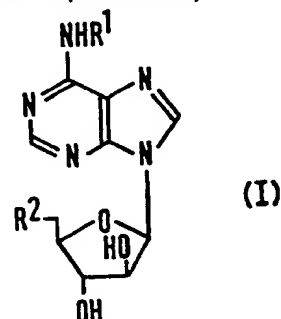
IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

- (21) Application No 8318159
(22) Date of filing 5 Jul 1983
(30) Priority data
(31) 57/119499
57/119500
(32) 8 Jul 1982
(33) Japan (JP)
(43) Application published
29 Feb 1984
(51) INT CL³
A61K 31/7031/52 31/66
45/06 //
C07H 19/20
(52) Domestic classification
A5B 180 190 216 21Y 230
23Y 281 28Y H J
C2P 2E13 2E15A 2E19D
2E26B 5B 7 9 A1 A
U1S 1313 1317 C2P
(56) Documents cited
EP 0048022 A
GB 1530912
GB 1444412
GB 1426469
GB 1381932
GB 1059764
EP 0066915 A
The Extra Pharmacopoeia
Martindale 27th Edition
1977 Pages 1828-1829
(58) Field of search
A5B
C2C
C2P
(71) Applicants
Yamasa Shoyu Kabushiki
Kaisha
(Japan),
10-1 Araoi-Cho 2 chome,
Choshi-Shi,
Chiba-Ken,
Japan
(72) Inventor
Shigekazu Nakatsugawa
(74) Agent and/or
Address for Service
F. J. Cleveland &
Company,
40-43 Chancery Lane,
London WC2A 1JQ

(54) Enhancer of anti-tumor effect

(57) 1- β -D-arabinofuranosyladenine derivatives represented by the formula (I):



wherein R¹ designates hydrogen or an acyl group and R² designates a hydroxyl group, a phosphoric acid residue or an alkyl- or alkenylphosphate residue; or pharmaceutically acceptable salts thereof are disclosed as being effective for enhancing anti-tumor effect afforded by irradiation to or administration of an anti-tumor pharmaceutical to tumor-bearing animals.

SPECIFICATION

Enhancer of anti-tumor effect

- 5 This invention relates to an enhancer of anti-tumor effect.

In the art of treatment of tumors, there have been many developments from various aspects. In radiotherapy, as a branch of these developments, there have also been attempts to improve the results of therapy. As one method, it is proposed to improve geometrical dose distribution by use of such methods as radiation of accelerated heavy ion particles or π meson. Another approach now under the development is to enhance selectively the sensitivity of tumor cells under hypoxic conditions, which are most resistant to radiotherapy among tumors, by utilizing a hypoxic cell sensitizer. Alternatively, combination treatments incorporating a method utilizing other anti-tumor factors, such as hyperthermia or chemotherapy have been attempted.

However, in the method for improvement of geometrical dose distribution, it is necessary to use enormous funds for installation of an accelerator and auxiliary equipments necessary for practicing the method as well as a large personnel including expert engineers and physicians. Other methods also involve drawbacks such as great damage to normal cells. For example, misonidazole, which is a hypoxic cell sensitizer, has neurotoxicity, and hence it is difficult to administer it in a large quantity, whereby no great radiosensitizing effect can be expected at concentrations available in clinical use, its effect being small in a low dose range (200 to 1,000 rad) as employed in a routine therapy.

On the other hand, in the field of chemotherapy of tumors, multiple anti-tumor agents have been combined to be used for the following purposes and effects:

1) By using in combination a number of different agents selected from those of alkylating agents, anti-metabolites, antibiotics and alkaloids, which show mutually no cross resistancy and are different in mechanism of action, the anti-tumor effect can be enhanced additively or synergistically against tumors which are composed of a mixture of tumor cells different in sensitivity to various agents.

2) By using in combination anti-tumor agents different in the way they attack tumor cells which are proliferating at random, various stages in the cell cycle of tumor cells can be widely attacked to ensure complete killing of tumor cells.

3) By using not only agents different in mechanism of action but also those having relatively similar mechanisms of action, a synergistic effort can be expected. For example, by using in combination a number of agents which are blocking a series of steps participating in DNA synthesis, a strong synergistic effect can be exhibited.

4) Each anti-tumor agent has its specific side effect. Thus, by using in combination a number of agents with different side effects each in a dosage less than the limit above which side effects appear, the anti-tumor effect can be expected to be increased additively or synergistically while the side effects are

dispersed.

By such a multi-agent combination treatment, it has been made possible to obtain an effect which could not be produced by using a single anti-tumor agent. However, each of the agents used in combination in such an application is an anti-tumor agent which can be independently used.

There have also been various attempts to use in combination with an anti-tumor agent a compound which does not *per se* have an anti-tumor effect for the purpose of strengthening the effect of the anti-tumor agent by preventing the anti-tumor agent from being inactivated in bodies. For example, it is known to use cytidine or uridine in combination with 1- β -D-arabinofuranosylcytosine (hereinafter referred to as "araC"), as disclosed in Japanese Patent Laid-Open Publication No. 24150/1980. It is also known to use tetrahydrouridine, which is an inhibitor against cytidine deaminase, in combination with araC, as disclosed in Cancer Research Vol. 30, pp.2166-2172, 1970. Further, there is known another method wherein 5-fluorouracil (hereinafter referred to as "5-FU") or a derivative thereof is combined with a pyrimidine compound such as, for example, uracil, cytosine, thymine, orotic acid, 5-bromouracil, 5-iodouracil, 1-acetyluracil, 1-(2-tetrahydrofuryl)-uracil, 3-benzoyluracil, 1-cyclohexycarbamoyluracil, 1-n-hexycarbamoyluracil, uridine, 2'-deoxyuridine, 5-bromo-2'-deoxyuridine, cytidine, or 2'-deoxycytidine.

On the other hand, in the field of radiotherapy, the tumor cells with radioresistance under hypoxic conditions are at a quiescent stage, and also there has been observed a phenomenon wherein potentially lethal damage repair (hereinafter referred to as "PLDR") is markedly manifested particularly in the cells at a quiescent stage. By inhibiting PLDR of such tumor cells, it is possible to increase the therapeutic effect of radiotherapy.

The PLDR phenomenon of tumor cells is observed not only in the field of radiotherapy but also in the treatment with a chemotherapeutic such as Bleomycin or 5-FU, as reported in the Journal of the National Cancer Institute, Vol. 50, No.2, pp.529-533, 1973.

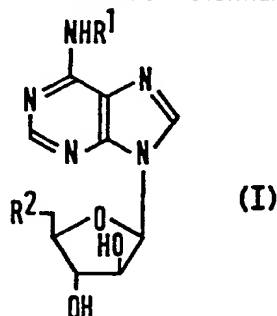
Accordingly, a pharmaceutical agent capable of inhibiting repair from damage of tumor cells can also enhance the anti-tumor effect not only of radiation but also of chemotherapeutics.

In view of the above described state of the art, we have made extensive studies with the aim of obtaining a radiosensitizing agent having a PLDR-inhibiting activity with low toxicity and good stability. As a result, it has now been found that a specified group of 1- β -D-arabinofuranosyladenine derivatives (hereinafter referred to as "araA derivatives"), particularly, N⁶-acyl-1- β -D-arabinofuranosyladenine derivatives (hereinafter referred to as "N⁶-acyl araA derivatives") and 1- β -arabinofuranosyladenine-5'-alkyl- or alkenyl phosphates (hereinafter referred to as "araAMP alkyl or alkenyl") have a PLDR-inhibiting activity and excellent radiosensitizing activity. It has also been found that these N⁶-acyl araA derivatives and araAMP alkyl or alkenyl can also exhibit excellent effect in strengthening anti-tumor effect in treatment of malignant tumors with chemotherapeutics. The

present invention has been accomplished on the basis of such findings. Thus, the present invention provides a pharmaceutical agent to be used for strengthening the antitumor effect in treatment of malignant tumors with radiation and/or an anti-tumor agent.

While the mechanism by which the pharmaceutical agent of the present invention acts on tumors has not yet been completely clarified, the present pharmaceutical agent may be considered to be a pharmaceutical which will enhance the anti-tumor effect of radiation or a chemotherapeutic through acting (e.g. inhibitory action) on changes in nucleic acid metabolism such as PLDR (e.g. repair of damage in DNA) caused by treatment with radiation or chemotherapeutics.

The present invention, in one aspect thereof, relates to a preparation of an enhancer of antitumor effect which comprises as an active component one or more araA derivatives of the formula (I):



wherein R¹ represents hydrogen or an acyl group and R² represents a hydroxyl group, a phosphoric acid residue or an alkyl- or alkenylphosphate residue, or pharmaceutically acceptable salts thereof.

The present invention, in another aspect thereof, relates to a chemotherapeutic composition for treating tumors which comprises an anti-tumor agent and one or more araA derivatives of the formula (I) or pharmaceutically acceptable salts thereof.

The present invention, in still another aspect thereof, relates to a method for enhancement of anti-tumor effect, which comprises administering to a tumor-bearing animal under an anti-tumor treatment an enhancer of anti-tumor effect which is an araA derivative of the formula (I) or a pharmaceutically acceptable salt thereof.

The term "animal" as herein used means a human being or a lower animal.

The wording "under an anti-tumor treatment" means the state wherein a tumor-bearing animal is being subjected to physical, chemical or physicochemical treatment for suppressing tumors or the state wherein there is retained in that animal an influence due to such a treatment. Accordingly and more specifically, the enhancer is administered to the animal before, simultaneously with, or after irradiation when the anti-tumor treatment comprises irradiation to a tumor site of the animal. The enhancer is administered before, simultaneously with, or after administration of an anti-tumor agent when the anti-tumor treatment comprises administration of an anti-tumor agent.

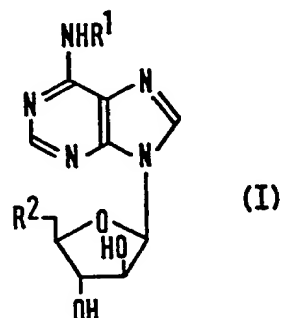
The present invention, in a further aspect thereof,

relates to a method for therapy of tumors which comprises administering to a tumor-bearing animal under an anti-tumor treatment an enhancer of anti-tumor effect which is an araA derivative of the formula (I) or a pharmaceutically acceptable salt thereof.

60 Enhancers

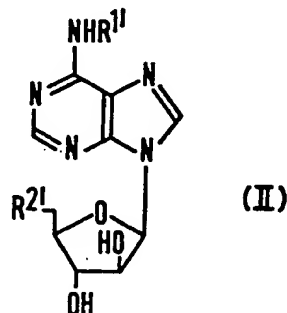
The enhancers in accordance with the present invention are araA derivatives of a specified group. The enhancers may alternatively be regarded as repair-inhibiting agents, and both terms are herein used interchangeably.

The araA derivatives are represented by the formula (I):



wherein R¹ designates hydrogen or an acyl group and R² designates a hydroxyl group, a phosphoric acid residue or an alkyl- or alkenylphosphate residue, or pharmaceutically acceptable salts thereof.

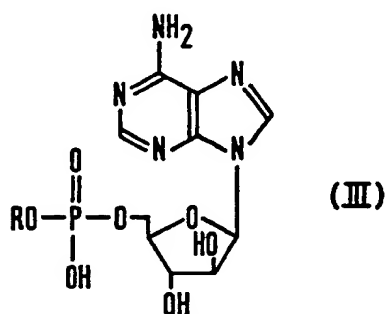
Typical examples of the araA derivatives are N⁶-acyl araA derivatives represented by the formula (II):



wherein R¹ designates an acyl group which preferably contains 2 to 26 carbon atoms and R² a hydroxyl group or a phosphoric acid residue.

More specific examples of the compounds may include N⁶-acetyl araA, N⁶-propionyl araA, N⁶-butyryl araA, N⁶-hexanoyl araA, N⁶-heptanoyl araA, N⁶-octanoyl araA, N⁶-nonanoyl araA, N⁶-decanoyl araA, N⁶-lauroyl araA, N⁶-palmitoyl araA, N⁶-stearoyl araA, N⁶-arachidonyl araA, N⁶-behenoyl araA, N⁶-oleoyl araA, N⁶-linoleoyl araA, and 5'-phosphoric acid ester derivatives thereof.

Other typical examples of the araA derivatives are araAMP alkyl or alkenyl represented by the formula (III):



wherein R designates an alkyl or alkenyl group which preferably contains 1 to 26 carbon atoms.

More specific examples of the compounds may include araAMP methyl, araAMP ethyl, araAMP propyl, araAMP butyl, araAMP pentyl, araAMP hexyl, araAMP heptyl, araAMP octyl, araAMP nonyl, araAMP dacyl, araAMP undecyl, araAMP lauroyl, araAMP tridecyl, araAMP tetradecyl, araAMP pentadecyl, araAMP cetyl, araAMP heptadecyl, araAMP stearyl, araAMP eicosyl, araAMP tricosyl, araAMP oleyl, and araAMP linoleyl.

Examples of the pharmaceutically acceptable salts of the araA derivatives are alkali metal salts such as those of lithium, sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, and ammonium salts.

The N⁶-acyl araA is a known compound (see Japanese Patent Pub. No. 5678/1978), and a 5'-phosphoric acid ester thereof can also be prepared by applying a known reaction, for example, by selectively phosphorylating the hydroxyl group at the 5'-position of araA to convert the araA into araAMP and acylating the araAMP.

The araAMP alkyl or alkenyl can be prepared by subjecting araAMP and an alkyl or alkenyl alcohol to a condensation reaction in an organic solvent.

Enhancement of anti-tumor effect

The pharmaceutical agent according to the present invention, when it is a preparation of an araA derivative alone, may be used for the purpose of enhancing the anti-tumor effect in the treatment of a malignant tumor, for which radiotherapy or chemotherapy by anti-tumor agents is to be applied, in combination with the treatments by these therapeutic methods.

In the case where the pharmaceutical agent of the present invention is used as a radiosensitizing agent for the purpose of enhancing the effect of radiotherapy, it may be administered before or after exposure, or even during exposure, if the occasion permits it, to the irradiation in radiotherapy. As to radiotherapy *per se*, the use of specific method and conditions is not required, but conventional radiotherapy techniques may be employed. By the use of the enhancer of the present invention in combination, it has become possible to apply radiotherapy with irradiation in the region of lower dosage than in the prior art. As the ionizing radiations for radio-therapy, those generally employed such as X-rays, linear high energy X-rays, betatron 32 MMeV electron beams or ⁶⁰Co-γ-rays may be used.

When used for the purpose of enhancing the anti-tumor effect in chemotherapy by an anti-tumor

agent, the enhancer of the present invention may be administered simultaneously with, after, or before administration of the anti-tumor agent. Anti-tumor agents, of which anti-tumor effects are to be enhanced by the pharmaceutical agent of the present invention, are exemplified typically by substances having activity similar to irradiations, including also those which can induce changes in nucleic acid metabolism such as repair phenomenon like PLDR in tumor cells on which an araA derivative can act after treatment therewith. Examples of anti-metabolites are methotrexate; 6-mercaptopurine; 5-FU and its derivatives, such as, for example, 5-fluorouridine, 5-fluoro-2'-deoxyuridine, 1-β-D-arabinofuranosyl-5-fluorocytosine, 1-(2-tetrahydrofuryl)-5-FU, 1-(n-hexylcarbamoyl)-5-FU, 1-ethoxymethyl-5-FU, 1-ethoxycarbonyl-5-FU, and 5-fluoro-5'-deoxyuridine; and araC and its derivatives, such as, for example, cyclocytidine, N⁴-palmitoyl araC, N⁴-stearoyl araC, N⁴-behenoyl araC, araC-5'-stearyl-phosphate, and araC-5'-oleylphosphate may be mentioned. Examples of anti-tumor antibiotics are Bleomycin; Neocarzinostatin; and Anthracycline type antibiotics, such as, for example, Daunomycin, Adriamycin, and Aclacinomycin. Examples of alkylating agents include nitrosourea, such as, for example, ACNU, BCNU, CCNU, MCNU; 3'-[3-(2-chloroethyl)-3-nitrosoureido]-3'-deoxythymidine; and 3'-(3-methyl-3-nitrosoureido)-3'-deoxythymidine. These anti-tumor agents may be administered by any method and in any dosage which are not specifically limited in combination with the enhancer of the present invention, but optimum conditions may suitably be selected for each agent used.

The pharmaceutical agent according to another aspect of the present invention, when it is a chemotherapeutic composition comprising an anti-tumor agent and an araA derivative in combination, can be prepared from one or more of the anti-tumor agents and the araA derivatives mentioned above in an appropriate ratio depending on the species of each constituent.

The pharmaceutical agents according to the present invention, irrespective of whether they are enhancers of anti-tumor agent or chemotherapeutic compositions, may comprise a pharmaceutically acceptable carrier. Examples of such carriers include lactose, magnesium stearate, talc, corn starch, "Witepsol" (Tradename, supplied by Dynamit Nobel Co., Germany), crystalline cellulose, distilled water, alcohols, and the like.

The method for administration of the pharmaceutical agent of the present invention may in general be either systemic administration or local administration. Various dosage unit forms can be selected depending on the purposes of therapy and the methods of administration. For example, as the form for systemic administration, an oral administration form such as tablet, capsule, granule or solution, or a non-oral administration form such as injection, suppository, etc., can be used. On the other hand, as a local administration form, a slow-releasing-capsule, an ointment or an injection can be used. In the preparing of such a dosage unit form, it is possible to make a preparation according to a conventional

method using a pharmaceutically acceptable carrier. Various modifications in preparation suitable for the object of the present invention may also be utilized.

The araA derivative of the present invention is used in an amount effective for enhancement of anti-tumor activity. More specifically, the dosage of the pharmaceutical agent of the present invention per day, which may slightly differ depending on the active ingredient employed, in general, is desirably 20 to 3,000 mg for an oral administration, 0.5 to 500 mg for an injection, and 20 to 2,000 mg for a suppository, as determined from basic experiments on anti-tumor effectiveness. The optimum effective amount should be determined by judgement of a physician according to the radiation used, its dosage, the anti-tumor agent used, its dosage, the conditions of disease, the affected part, etc.

The pharmacological effects of the pharmaceutical agents of the present invention are shown below with data from the tests of radiosensitizing effect and anti-tumor effect enhancing effect thereof.

Experiment 1

Radiosensitizing effect on experimental tumor in mice

SQ₁ tumor cells were inoculated intradermally into the right thighs of C3H/Heston-strain mice. When the tumor size reached 5 to 10 mm in diameter, the mice were locally irradiated with Lineac 10 MeV X-rays at 1,500 rad and thereafter a compound to be tested was administered intraperitoneally to each mouse at a

dose level of 100 mg/kg.

On the 42nd day after the irradiation, the tumor sizes were measured and the mean tumor diameter was derived from the mean of the longitudinal diameter, lateral diameter and height of the tumor while the diameter ratio was determined by the ratio of the mean tumor diameter thus derived to that measured at the time of irradiation. Subsequently, the mean tumor volume ratio was obtained from the cube of the diameter ratio thus determined.

For the control group which was subjected to X-ray irradiation alone, the mean tumor volume ratios were similarly obtained at 1,500 rad, 2,000 rad, and 2,500 rad. By plotting the doses of X-rays and the mean tumor volume ratios of the control group on the graph and estimating the radiosensitizing effect of the group which was subjected to X-ray irradiation and also treated with a compound to be tested in terms of the doses of X-rays using the dose-effect calibration curve obtained, the radiosensitivity ratio was derived from the ratio of the dose of X-rays indicating the estimated radiosensitizing effect to 1,500 rad.

The results are summarized in Table 1. The compounds to be tested *per se*, when administered once at a dose level of 100 mg/kg, do not exhibit a significant effect in inhibiting the growth of SQ₁ cancer cells, but, when administered in combination with irradiation with X-rays at 1,500 rad, exhibited a marked radiosensitizing effect.

Table 1

X-ray dose (rad)	Compound to be tested (100mg/kg)	Average tumor volume ratio	X-ray dose indicating estimated radiosensitizing effect	Radiosensitivity ratio
2500	-	2.69±1.93	-	-
2000	-	8.42±5.28	-	-
1500	-	15.68±3.83	-	-
1500	N ⁶ -butyryl araA	10.01±1.54	1900	1.27
1500	N ⁶ -octanoyl araA	7.81±1.08	2070	1.38
1500	N ⁶ -behenoyl araA	3.69±1.58	2390	1.59
1500	araAMP butyl	9.94±2.09	1900	1.27

Experiment 2

Enhancement of the effect of anti-tumor agents on experimental tumors in mice

SQ₁ tumor cells were inoculated intradermally into the right thighs of C3H/Heston-strain male mice. When the tumor sizes reached 5 to 8mm in diameter, ACNU was administered intraperitoneally to each mouse at a dose level of 12 mg/kg, and 1 hour thereafter, a compound to be tested was similarly administered at a dose level of 32 mg/kg. The mice were thus treated once a day for five consecutive days, and on the 21st day after the initiation of these treatments, the tumor sizes were measured. The results were as shown in Table 2.

Table 2

Run No.	Anti-tumor agent (12 mg/kg)	Compound to be tested (32 mg/kg)	Mean tumor volume ratio
1	(Control) -	-	7.51 ± 4.23
	ACNU	-	7.17 ± 0.87
	-	N ⁶ -butyryl araA	15.31 ± 4.53
	-	N ⁶ -octanoyl araA	18.23 ± 3.44
	-	N ⁶ -behenoyl araA	8.69 ± 2.19
	-	araAMP butyl	8.51 ± 0.74
	ACNU	N ⁶ -butyryl araA	5.48 ± 1.85
	ACNU	N ⁶ -octanoyl araA	4.03 ± 0.86
	ACNU	N ⁶ -behenoyl araA	4.44 ± 0.68
2	ACNU	araAMP butyl	4.13 ± 0.37
	(Control) -	-	9.73 ± 2.28
	ACNU	-	9.00 ± 1.95
	-	araAMP octyl	7.54 ± 2.09
	-	araAMP stearyl	9.46 ± 2.10
	ACNU	araAMP octyl	3.90 ± 0.63
	ACNU	araAMP stearyl	3.67 ± 0.67

Preparation Example 1

Twenty (20) mmol of n-butanol was dissolved in 30 ml of a pyridine solution containing 10 mmol of N⁶, O^{2'}, O^{3'} - triacetyl araAMP, and the resulting solution was caused to react with 20 mmol of tosyl chloride.

To the solution obtained was added 20 ml of ammonium hydroxide for deacetylation. After the deacetylation, the resulting solution was concentrated and then water was added to form 2 l of a solution which was applied on 200 ml of a strongly basic anion exchange resin (Dowex 1 × 5 (formic acid form)) packed in a column. Thereafter, elution was conducted with 0.02N formic acid and then with 0.5N formic acid. Fractions of the desired compound were collected and concentrated. To the concentrate was added acetone to form a precipitate which was dissolved in water and then concentrated. To the concentrate was again added acetone to form a precipitate. To this precipitate was added ethanol, and the mixture was heated, stirred, cooled, filtered and dried to obtain 1.6 g of araAMP butyl.

Melting point 173°C (decomposed)

Ultraviolet absorption

$E_{1\%}^{1\text{cm}}$ (259nm, pH 7.0) 367

25 $OD_{250/260} = 0.80$

$OD_{280/260} = 0.13$

Preparation Example 2

Twenty (20) mmol of n-octanol was dissolved in 30 ml of a pyridine solution containing 10 mmol of N⁶, O^{2'}, O^{3'} - triacetyl araAMP, and the resulting solution was caused to react with 20 mmol of tosyl chloride.

Water and chloroform were added to the solution obtained, and the mixture was stirred and then separated into individual ingredients. Ammonium

hydroxide was added to the chloroform solution thus separated to deacetylate the reaction product dissolved therein. After the deacetylation, the resulting solution was concentrated, and then water and chloroform were added to the concentrate to isolate an aqueous layer. The aqueous layer thus isolated was concentrated to form a precipitate which was separated by filtration. This precipitation was dissolved in water and adjusted to an acidic pH to form a precipitate. To the precipitate formed was added ethanol, and the mixture was stirred, filtered and dried to obtain 0.6 g of araAMP octyl.

Melting point 185°C (decomposed)

Ultraviolet absorption

$E_{1\%}^{1\text{cm}}$ (259 nm, pH 7.0) 305

50 $OD_{255/260} = 0.78$

$OD_{280/260} = 0.15$

Preparation Example 3

Twenty (20) mmol of stearyl alcohol was dissolved in 30 ml of a pyridine solution containing 10 mmol of N⁶, O^{2'}, O^{3'} - triacetyl araAMP, and the resulting solution was caused to react with 20 mmol of tosyl chloride.

Water and chloroform were added to the solution obtained, and the mixture was stirred. A layer of chloroform was formed and was isolated, and ammonium hydroxide was added thereto to deacetylate the reaction product dissolved therein. After the deacetylation, to the resulting solution was added water for extraction, and the extract was adjusted to an acidic pH to form a precipitate. The precipitate thus formed was separated by decantation, ethanol added thereto, the mixture stirred, and the precipitate separated by filtration. This precipitate was dissolved

in water under neutralizing conditions, and acidified again to form a precipitate which was separated by filtration, washed with water and ethanol, separated again by filtration and dried to obtain 2.1 g of araAMP

5 stearyl.

Melting point 180°C (decomposed)

Ultraviolet absorption

$E_{1\%}^{1\text{cm}}$ (259 nm, pH 7.0) 217

OD_{250/260} = 0.80

10 OD_{280/260} = 0.27

Formulation Example 1

N ⁶ -butyryl araA	100mg
Lactose	170mg
Magnesium stearate	3mg
Crystalline cellulose	57mg
<hr/>	
	330mg/ capsule

Capsules are prepared according to the above formulation.

Formulation Example 2

N ⁶ -octanoyl araA	100mg
Lactose	100mg
Magnesium stearate	2mg
Talc	3mg
Hydroxypropylmethyl cellulose	10mg
<hr/>	
	215mg/ tablet

Tablets are prepared according to the above formulation.

Formulation Example 3

N ⁶ -behenoyl araA	500mg
Lactose	240mg
Corn starch	250mg
Hydroxypropylmethyl cellulose	10mg
<hr/>	
	1,000mg/ package

Granules are prepared according to the above formulation.

Formulation Example 4

N ⁶ -butyryl araA	100mg
Tris-amino methane	220mg
Distilled water for injection	appropriate amount
<hr/>	
	10ml/ ampoule

Injectons are prepared according to the above formulation.

Formulation Example 5

N ⁶ -behenoyl araA	500mg
Witepsol W-35	1,500mg

2,000mg/
suppository

Suppositories are prepared according to the above formulation.

Formulation Example 6

N ⁶ -butyryl araA	50mg
ACNU	50mg
Sodium carbonate	440mg
Sodium hydroxide	35mg
Distilled water for injection	appropriate amount

10ml/
ampoule

Injections are prepared according to the above formulation.

Formulation Example 7

araAMP stearyl	100mg
Lactose	170mg
Magnesium stearate	3mg
Crystalline cellulose	57mg

330mg/
capsule

Capsules are prepared according to the above formulation.

Formulation Example 8

araAMP stearyl	100mg
Lactose	100mg
Magnesium stearate	2mg
Talc	3mg
Hydroxypropylmethyl cellulose	10mg

215mg/
tablet

Tablets are prepared according to the above formulation.

Formulation Example 9

araAMP stearyl	500mg
Lactose	240mg
Corn starch	250mg
Hydroxypropylmethyl cellulose	10mg

1,000mg/
package

Granules are prepared according to the above formulation.

Formulation Example 10

araAMP butyl	100mg
Tris-amino methane	220mg
Distilled water	
for injection	appropriate amount
<hr/>	
	10ml/ ampoule

Injectons are prepared according to the above formulation.

Formulation Example 11

araAMP stearyl	500mg
Witepsol W-35	1,500mg
<hr/>	
	2,000mg/ suppository

Suppositories are prepared according to the above formulation.

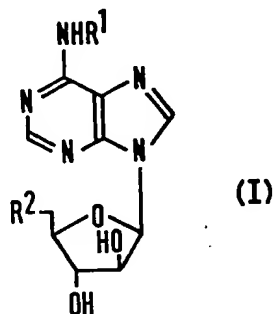
Formulation Example 12

araAMP butyl	50mg
ACNU	50mg
Sodium carbonate	440mg
Sodium Hydroxide	35mg
Distilled water	
for injection	appropriate amount
<hr/>	
	10ml/ ampoule

Injectons are prepared according to the above formulation.

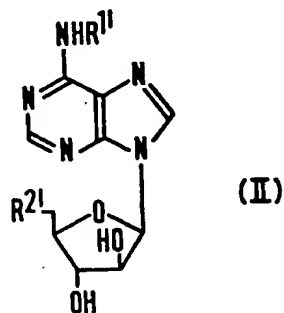
CLAIMS

1. A preparation of an enhancer of anti-tumor effect which comprises as an active component:
one or more 1- β -D-arabinofuranosyladenine
5 derivatives represented by the formula (I):



wherein R^1 designates hydrogen or an acyl group and R_2 designates a hydroxyl group, a phosphoric acid residue or an alkyl- or alkenylphosphate residue; or pharmaceutically acceptable salts thereof.

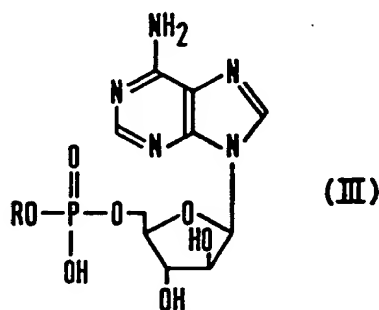
- 10 2. The preparation as claimed in claim 1 in which the 1- β -D-arabinofuranosyladenine derivative is an N^6 -acyl-1- β -D-arabinofuranosyladenine derivative represented by the formula (II):



wherein R^1 designates an acyl group and R^2 designates a hydroxyl group or a phosphoric acid residue; or
15 a pharmaceutically acceptable salt thereof.

3. The preparation as claimed in claim 2 in which the substituent R^1 is an acyl group which contains 2
20 to 26 carbon atoms.

4. The preparation as claimed in claim 1 in which the 1- β -D-arabinofuranosyladenine derivative is a 1- β -D-arabinofuranosyladenine-5'-alkyl- or alkenylphosphate represented by the formula (III):



wherein R designates an alkyl or alkenyl group; or a pharmaceutically acceptable salt thereof.

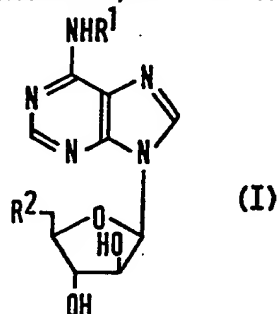
5. The preparation as claimed in claim 4 in which the substituent R is an alkyl or alkenyl group which contains 1 to 26 carbon atoms.

6. A chemotherapeutic composition for treating tumors which comprises:

an anti-tumor agent; and

one or more 1-beta-D-arabinofuranosyladenine

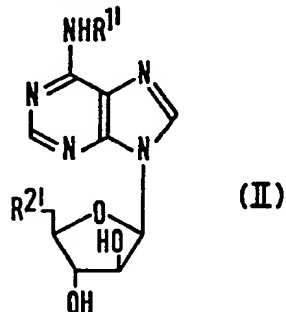
10 derivatives represented by the formula (I):



wherein R¹ designates hydrogen or an acyl group and R² designates a hydroxyl group, a phosphoric acid residue or an alkyl- or alkenylphosphate residue; or pharmaceutically acceptable salts thereof.

15 7. The chemotherapeutic composition for treating tumors as claimed in claim 6 in which the anti-tumor agent is selected from the group consisting of anti-metabolites, anti-tumor antibiotics and alkylating agents.

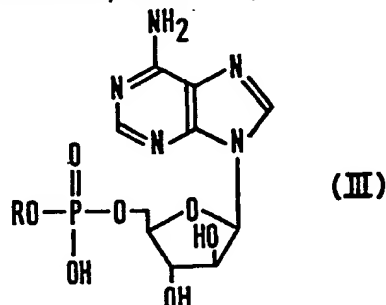
20 8. The chemotherapeutic composition for treating tumors as claimed in claim 6 in which the 1-beta-D-arabinofuranosyladenine derivative is an N⁶-acyl-1-beta-D-arabinofuranosyladenine derivative represented by the formula (II):



25 wherein R^{1'} designates an acyl group and R^{2'} designates a hydroxyl group or a phosphoric acid residue; or a pharmaceutically acceptable salt thereof.

9. The chemotherapeutic composition for treating tumors as claimed in claim 8 in which the substituent R^{1'} is an acyl group which contains 2 to 26 carbon atoms.

10. The chemotherapeutic composition for treating tumors as claimed in claim 6 in which the 1-beta-D-arabinofuranosyladenine derivative is a 1-beta-D-arabinofuranosyladenine-5'-alkyl- or alkenylphosphate represented by the formula (III):



wherein R designates an alkyl or alkenyl group; or a pharmaceutically acceptable salt thereof.

40 11. The chemotherapeutic composition for treating tumors as claimed in claim 10 in which the substituent R is an alkyl or alkenyl group which contains 1 to 26 carbon atoms.

12. A preparation as claimed in claim 1 and 45 substantially as herein described with reference in any one of the specific examples hereinbefore set forth.

Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd.,
Berwick-upon-Tweed, 1984.
Published at the Patent Office, 25 Southampton Buildings, London
WC2A 1AY, from which copies may be obtained.